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THE EFFECT OF ROENTGEN RAYS ON SKIN REACTIVITY TO HISTAMINE AND BACTERIAL VACCINE

With Review of the Literature and a Discussion of the Mode of Action of the Roentgen Rays in Inflammatory Processes[1]

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INTRODUCTION

Ever since it was appreciated that roentgen rays exert a favorable therapeutic effect on many inflammatory conditions, attempts have been made to explain this action on the basis of experimental and clinical findings. Much work has been done in these fields and many important facts have been learned (1–16), but the basic action of roentgen rays in inflammatory disease is still unknown.

The present work deals with the problem of how roentgen rays modify the reaction properties of the skin. This problem is of importance in that it may possibly throw some light on the basis of the behavior of the roentgen rays in inflammatory conditions and thus lead to a more rational therapy.

Generally speaking, the skin shows three principal types of acute response to trauma:

(1) The eczematous reaction with its spongiosis and vesicula-

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vestigated clinically by MacKee and Andrews (18) and experimentally by Pfahler, Klauder and Martin (19). These workers concluded that ultraviolet light reactions are increased by either previous or subsequent roentgen ray exposures of the skin.

Zurhelle (21) arrived at a similar conclusion, using radium instead of roentgen rays. The same author also studied the effect of solid carbon dioxide (here the corium is, of course, also injured). He noted that the reaction to this agent was much enhanced when it was applied to an area of skin rendered erythematous by the application of a radium plaque ten days previously.

Primary skin irritants, such as mustard oil, have been shown by Schwarz (22) to produce stronger reactions both on roentgen rayed as well as radium treated areas than on normal skin, while Zurhelle (21) showed a similar effect on using radium.

Allergic sensitization such as is present in contact-type eczematous dermatitis and such as can be demonstrated by patch tests also is enhanced by previous irradiation of the skin. This was demonstrated by Zurhelle (21) using a nickel chloride patch test in a patient who was sensitive to nickel, and also with an iodide patch test in a patient suffering with dermatitis herpetiformis.

The whealing reaction.

Studies on the whealing reactions of irradiated skin were conducted by Sir Thomas Lewis (23) who reported that, following erythema produced by exposures of the skin to either roentgen rays or radium, the histamine wheal either failed to develop or was greatly suppressed. Zurhelle (21) also made similar studies on skin rendered erythematous by exposure to radium ten days previously. He found that not only was the histamine wheal suppressed, but also that the flare which surrounds the wheal was less marked and tended to disappear more rapidly. He pointed out, furthermore, that reactions of the skin which are physiologically and pathologically similar to the histamine wheal, such as reactions to the intracutaneous introduction of protein allergens, the edematous component of the von Pirquet and the Dmelcos tests, and the traumatic edema following scarification—all these reactions—behave in a manner similar to the histamine wheal on radium irradiated skin.

The papular reaction.

The influence of roentgen rays on papular inflammatory reactions of irradiated skin were studied most extensively in the case of the tuberculin reaction. Nista, Jovin, and Bleckman (24) found that the tuberculin reaction in tuberculous guinea pigs, both in the irradiated as well as in the non-irradiated skin areas, was diminished following large doses of roentgen rays. This, of course, indicates a general systemic effect rather than a purely local reaction. Liebersohn and Schimako (25) reported that the von Pirquet test, performed on human skin, was decreased in 70 per cent of the cases after large doses of roentgen rays, while it was greatly increased after fractional roentgen-ray exposures. The maximum effect was noted seven to fourteen days following irradiation while no effect could be observed after a period of twenty-one days. In three cases a dilute solution of

tuberculin failed to produce a reaction, but after irradiation of the skin with a single fractional dose of roentgen rays, the test became positive. Bonano (26) found that many patients with a negative tuberculin reaction became tuberculin positive after radiotherapy for various maladies. Here, again, one is dealing with a systemic rather than a local effect. The author considered this phenomenon in the nature of a non-specific stimulation of tuberculin sensitivity. Zurhelle (21), using an erythema-producing exposure of radium ten days previously, could not find any difference in the "late" reactions of the skin to ascarides antigen, trichophytin, or the post-edematous phase of the Dmelcos test.

Thus, it is seen that after erythema-producing doses of either roentgen rays or radium, the eczematous skin reactions are enhanced, the whealing and edematous reactions of the skin are diminished, while the results of experiments in the case of the papular inflammatory and allergic "late" reactions of the skin apparently differed at the hands of the several investigators. As far as I could find, except for the work of Liebersohn and Schimako, the literature does not contain reports of cases in which roentgen rays or radium was employed in amounts less than an erythema-producing dose.

Other cutaneous reactions. It may be of interest to note the effect of preceding roentgen rays on other reactions of irradiated skin, which while not primarily inflammatory in type, might help to throw some further light on the present problem.

Meyer and Mutscheller (27) found that if skin heated by diathermy is simultaneously or subsequently irradiated with roentgen rays, a skin erythema dose can be administered in less time, and with a less intense roentgen ray beam than if irradiation is employed alone. These authors therefore conclude that heat "sensitizes" the skin to roentgen rays. A similar effect has been reported with reference to tissue cultures (28, 29) and also in experimental tumors (30, 31).

Neu (32) measured the electrical conductivity of the human skin following roentgen ray exposures. He observed that conductivity was increased as early as two days, and as late as several weeks following the application of the rays, and that this increased conductivity could be demonstrated before the time of appearance of the erythema.

That roentgen rays produce effects on the skin which follow a cyclic or wave-like course has been appreciated for some time. This was originally pointed out by Miescher (33) who, from astute clinical observations, reported on the wave-like character of the erythema appearing subsequent to roentgen ray exposures of the skin. He described three separate waves with average peaks at two, fifteen, and thirty-nine days. Miescher emphasized that the latent periods between these waves were apparent rather than real, inasmuch as they tended to disappear with heavier doses.

Williams and Sheard (34) made observations of the changes in electrical potential and the rate of oxidation on the frog's skin after roentgen ray exposures. They reported that both of these factors were increased but they also observed that the changes occurred in a cyclic or wave-like manner up to a period of thirty days, after which both measurements fell below normal.

Pohle (35) employed the capillary microscope to study the behavior of the capillaries in roentgen ray irradiated skin. The skin was prepared by treating it with a single exposure of the unfiltered roentgen ray of either one-half or one erythema dose. He was able to detect capillary dilatation and an increase in the number of visible capillaries as early as six hours after irradiation. These capillary effects, on serial observation, were found to follow a phasic or cyclic course paralleling quite faithfully the clinically visible erythema. However, as Pohle pointed out, many changes in capillary behavior were not detectable in the visible erythema, so that he felt that capillary microscopy was a much more delicate method of detecting roentgen ray effects than was the clinical appearance of the skin. Three separate waves were described with maxima at six hours to two days, six days to ten days, and at twenty days. When Pohle used filtered radiation in a later study (36), he noted a similar effect on the skin capillaries, except that the cyclic phenomenon was much less pronounced.

Harris, Leddy and Sheard (37) used a spectrophotometric method for analyzing skin color changes in order to study objectively the features of the waves of erythema following roentgen ray irradiation of the skin. They used a dosage of 525 r of filtered radiation and confirmed the reports of previous investigators.

Much evidence, therefore, points to the fact that roentgen ray irradiation of the skin results in cyclic changes in behavior, not only with reference to metabolism, but especially in regard to capillary activity. The latter changes are paralleled by, and result in waves of erythema, which ordinarily are not detectable clinically, but which can be determined by serial capillary microscopy or by spectrophotometric examination of skin color. It seems also probable that the time of appearance of the waves, their intervals, maxima, and durations vary in different subjects (37) and according to the degree of hardness of the rays (36) and to the dosage and intervals between doses.

As early as 1915, it was noted by Ricker (39) that the smaller blood vessels of the skin are quite sensitive to roentgen ray effects. This is illustrated quite well by the following studies.

In a number of instances Hodes (40), using the capillary microscope, was able to distinguish capillary dilatation as early as four hours following exposure of the skin to a dosage of 300 r. As mentioned above, Pohle found not only dilatation but also an increase in the number of visible capillaries after an interval of six hours.

Another early effect of roentgen rays on skin capillaries is change in permeability. Mottram (41) exposed a small portion of the skin of the rat to one erythema dose of roentgen rays. Immediately thereafter he injected a solution of pyrrhol blue into the circulation. The next morning he found a blue mark corresponding to the irradiated site. He concluded that the roentgen rays apparently altered the skin capillaries so that the dye passed through them more readily. It was mentioned above that the histamine wheal is suppressed on skin rendered erythematous by irradiation. Lewis (23) attributes this phenomenon to the fact that the "minute vessels of the skin" are in a histamine refractory state with reference to their permeability.

According to Pohle (35) the reaction of skin capillaries to heat and cold tends to be greatly diminished during the cyclic periods when they are dilated subsequent to a roentgen ray exposure. This response tends to return in the intervals between the waves.

Therefore, it seems quite obvious that the skin capillaries are profoundly affected by roentgen rays and that they are highly susceptible to radiation effects. It is quite probable that roentgen ray effects on capillaries play an important role in determining the action of roentgen rays in inflammatory states. However, this matter will be discussed later in greater detail.

EXPERIMENTAL DATA

The present investigation deals with the effect of roentgen rays in modifying the reactions of the skin to injections of histamine and vaccine.

Methods of procedure. The subjects were twenty-four adults (twelve white and twelve negro, fifteen men and nine women) of whom eighteen were under treatment for latent syphilis while the remaining six suffered from minor dermatoses which did not involve regions of the skin used in this experiment.

Roentgen ray exposures were made only to the left side of the back of each subject while the right side was completely protected by lead-rubber. The sites irradiated on the left side of the back consisted of eight squares, each one 1″ x 1″ (2.5 cm. x 2.5 cm.) in size, arranged in two vertical rows of four squares (see figure 1). The squares were so spaced that their centers were three inches apart. The intervening skin was protected by covering the left side of the back with a sheet of lead-rubber, in which square openings had been cut to correspond in size and position to the squares of skin which were to be subjected to the radiation.

In order that each square might receive an equal amount of irradiation, the center of the roentgen ray beam was directed first to a point corresponding to the hypothetical center of a circle marked out by the centers of the upper four squares. During this time, the lower four squares were protected by lead-rubber. A similar technic was then employed in irradiating the lower four squares.

Each exposure consisted of 125 r with a skin-anode distance of twelve inches (30.5 cm.). The roentgen rays were unfiltered and were generated at 100 Kv, using a mechanically rectified tube current of two milliamperes. The half value layer aluminum of the roentgen ray beam was 0.88. Each exposure lasted two and a half minutes so that the intensity of the beam at the skin surface was 50 r per minute.

On subjects 1 to 12 inclusive each irradiated square received a single dose of 125 r. On cases 13 to 24 inclusive the squares received three such exposures at daily intervals to make a total of 375 r. The irradiation was distributed over a period of three days so that a clinical roentgen ray erythema might not occur since this might interfere with the readings of the experimental injections.

At different times, from one hour to five days following the completion of the irradiation, a 1:1000 solution of histamine phosphate was injected in the center of each square comprising the lateral vertical row of squares. A stock catarrhal vaccine[5] was injected into the centers of the medial row of four squares at similar

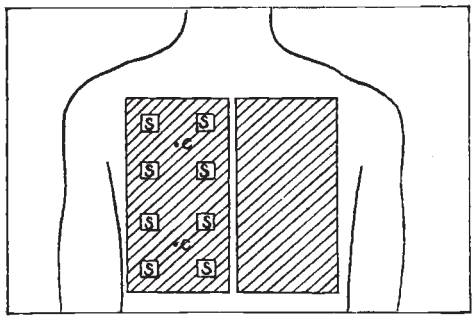


FIG. 1. S = Square 1″ x 1″ cut out of lead-impregnated rubber. Each square is spaced equidistant from its neighbors so that the centers are 3 inches apart.

C = Point at which the center of the X-ray beam was directed when exposures were being made.

intervals. Symmetrical non-irradiated sites on the opposite of the back were similarly injected, in order to serve as controls.

Following the histamine injections, readings were made at two, five, fifteen, and thirty minutes measuring the size of the wheal in millimeters by recording the

[5] Manufactured by the National Drug Company, Philadelphia, and consisting of 2000 million bacteria per cc. divided as follows:

Name of the bacteria	*Each cc. contains*
M. catarrhalis group	200 million
Staphylococcus (*aureus* and *albus*)	200 million
Streptococcus (*hemolyticus* and *viridans*)	500 million
B. influenzae (Pfeiffer)	500 million
Pneumococcus (Type I, II, III, IV)	500 million
B. Friedlander	100 million

longest diameter and the diameter at right angles to this (pseudopods were not included in these measurements). At the same intervals, measurements were taken also of the size of the flare (in centimeters) and the intensity of the erythema in the flare (as estimated in degrees of plus 1 to plus 4) in subjects 16 to 24 inclusive. The squares in cases 1 to 15 inclusive were injected with 0.1 cc. of the histamine solution while 0.05 cc. was used in subjects 16 to 24 inclusive.

Subjects 13 and 15 to 24 inclusive received vaccine injections in a dosage of 0.1 cc. Readings of the size of the papules were made at daily intervals over a period of one to nine days. The readings consisted in measuring the two opposite diameters and the height of the papule, and recording these in millimeters.

In order to analyze the foregoing readings statistically, and for the purpose of illustrating certain findings graphically, it was found necessary to express the size of the histamine wheal and the vaccine papule as a single number. Accordingly, the size of the histamine wheal was calculated to be the average of its two diameters, while the size of the vaccine papule was computed from the average of its two diameters multiplied by its height.

EXPERIMENTAL RESULTS

Histamine injections. Table I is a compilation of the results when histamine was injected into roentgen ray irradiated and non-irradiated skin. Only the greatest figure which was obtained over an observation period of thirty minutes following the injection of the histamine is recorded on this table. Therefore, analyses of histamine action derived from this source represent the maximal effect noted for each injection.

Size of wheal. A study of this table demonstrates that, under the conditions of this investigation, the histamine wheal tends to be smaller on roentgen rayed skin than on non-irradiated skin. (See also graphs I and II.) This table also shows that the flare surrounding the histamine wheal tends to be smaller in size and less intense in its degree of erythema on the irradiated site than on the control skin.

Thirty-seven experiments were performed in which histamine was injected in skin exposed to 375 r (divided over a period of three daily exposures of 125 r) (Table II). The average size of the wheal on the roentgen-rayed skin was 15.7 mm., while the wheal on the control sites averaged 18.3 mm. Another series of twenty experiments was similarly performed on skin exposed to a single dose of 125 r. When these two groups were averaged (comprising a total of fifty-seven experiments), the average wheal on the roentgen-rayed skin measured 16.2 mm.,

while the wheal on the non-irradiated site measured 18.3 mm. These groups included readings made at one, two, three, four, and five days after a single exposure of 125 r and one hour, one, two, three, four, and five days after a final exposure of 375 r (i.e. three, four, five, six, seven, and eight days after the initial exposure). From these figures one can conclude that the histamine wheal is reduced when the injection is made from two to five days after a roentgen ray exposure.

Size and intensity of flare. Table I presents evidence showing that the flare which develops about the histamine wheal is markedly diminished by irradiation. This applies to size as well as intensity of erythema. The size of the flare was measured and observed over a period of thirty minutes in twenty-nine experiments. The largest size to which it developed during this period was averaged. The average flare on the roentgen-rayed skin measured only 1.9 cm. as contrasted to 3.0 cm. on the control skin. Similarly, readings on the intensity of the erythema in the flare were estimated in twenty-eight instances. Here the degree of erythema averaged 1.3 on the irradiated skin as compared to 2.4 on the non-irradiated site.

Vaccine injections. When 0.1 cc. of vaccine was injected into the center of squares of skin which had been irradiated with three daily successive roentgen ray doses of 125 r each, it was found that the papule which developed on the irradiated site was, in general, larger than that which developed on the control area. It will be noted that this behavior is just the opposite of that found in the case of the histamine wheal.

Vaccine papule: rate of regression. Table III gives a compilation of the data relevant to the vaccine studies, based on the size of the papule as calculated from readings made daily following the injection. The injections were made at one hour, one, two, three, four, and five days after the last roentgen ray exposure. Table III groups these readings, not with reference to the time interval between the roentgen ray exposures and the injection, but with regard to the period between the injections of the vaccine and readings of the size of the papule. Thus all papules measured the first day after injection are placed in one

TABLE I

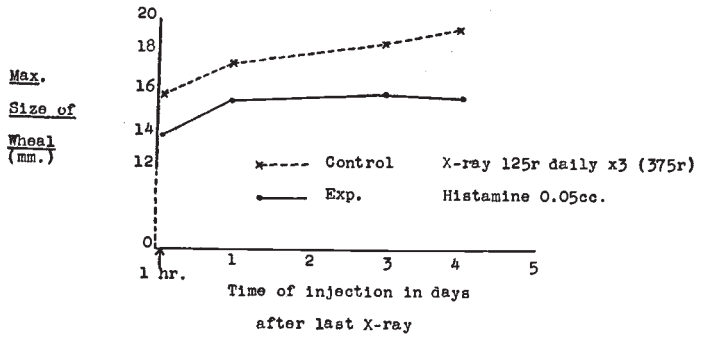
Differences in reactivity of x-rayed and normal skin to histamine

Interval between last x-ray and injection	X-ray 125 r daily for 3 days = 375 r													X-ray 125 r histamine 0.1 cc.				
	Histamine 0.05 cc.												Histamine 0.1 cc.					
	Case number	Maximum* size of wheal (mm.)				Maximum* size of flare (cms.)				Maximum* degree of erythema in flare				Case number	Maximum* size of wheal (mm.)		Case number	Maximum* size of wheal (mm.)	
		Experimental		Control		Experimental		Control		Experimental		Control			Experimental	Control		Experimental	Control
		Reading	Average	Reading	Average	Reading	Average	Reading	Average	Reading	Average	Reading	Average		Reading	Reading		Reading	Reading
1 hour	17	11.5	14.5	14.0	16.0	3.0	1.8	4	2.9	0.5	0.5	2	2.7	13	19.0	21.0			
	18	14.0		16.0		1.0		3		—		—		14	19.0	16.5			
	22	17.5		17.5		3.0		3		2		4		15	17.5	21.5			
	23	16.0		16.0		2.0		3		1		3							
	24	13.5		13.5		2.5		2		1		3							
	16	13.0		21.0		1.0		3		1		3							
	19	11.5		13.0		0		3		0		2							
	21	14.0		17.5		2.0		2		1		2							
1 day	16	20.0	15.6	17.5	17.5	2	1.4	4	2.8	1	0.6	2	1.8	13	20.0	22.0	2	14.0	12.0
	17	15.5		18.5		0		2		0		2		15	16.0	18.0	3	12.5	14.0
	18	15.0		15.0		3		4		1		2							
	19	14.5		17.5		0		2		0		1							
	21	13.0		19.0		2		2		1		2							

2 days	22	18.0		23.0		3		2		1		3		13	16.0	27.5	2 3 4 5 6 7 8	17.0 17.5 16.5 16.5 19.0 18.0 18.0	17.5	22.0 20.0 16.0 16.5 19.5 19.5 18.0	18.8
3 days	16 17 18 19 20 23	15.5 16.5 16.5 16.5 15.0 16.0	16.0	17.5 20.0 16.0 19.5 16.0 22.0	18.5	1 2 3 0 3 3	2.0	4 3 4 2 3 3	3.2	1 1 1 0 2 3	1.3	1 2 3 2 3 3	2.3	13	16.5	19.5	2 3 4 5	20.0 18.5 17.0 17.0	18.1	19.0 19.0 18.0 18.0	18.5
4 days	16 18 19 20 21 22 24	22.0 15.0 14.5 17.5 13.5 10.0 18.0	15.8	19.0 16.5 19.0 18.0 19.5 15.5 18.5	19.4	2 2 0 3 3 1 2	1.9	3 3 4 3 4 2 3	3.1	2 2 0 2 1 3 3	1.9	2 3 2 3 2 2 3	2.4	14	14.0	14.5	2 3 4 5	15.0 15.0 18.0 16.0	16.0	17.5 17.0 18.0 16.0	17.0
5 days	17 20	12.0 18.0		23.0 17.5		2 4		4 4		2 2		2 3					4 6 9	22.0 16.0 16.0	18.0	22.0 16.0 17.0	18.3
Number of readings....		29		29		29		29		28		28			8	8		20		20	
Total average.....		15.3		17.8		1.9		3.0		1.3		2.4			17.3	20.1		17.0		18.3	

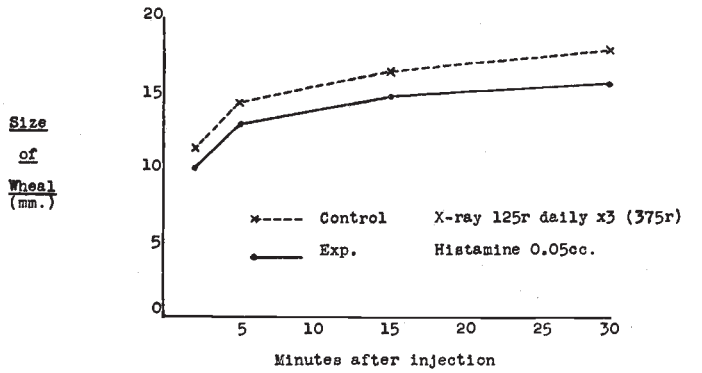
* Each figure recorded here represents the greatest reading made over an observation period of 30 minutes following injection of the histamine. Averages are calculated only when three or more figures are recorded.

category irrespective of whether they were injected one hour, or five days following the last roentgen ray exposure. The



GRAPH 1. RELATIONSHIP BETWEEN THE MAXIMUM SIZE OF THE HISTAMINE WHEAL AND THE TIME INTERVAL BETWEEN THE LAST ROENTGEN RAY EXPOSURE AND THE INJECTION

0.05 cc. of histamine was injected at one hour and at 1 to 4 days after 3 daily exposures of 125 r each. The histamine wheal on the roentgen rayed skin is seen always to be smaller than on the non-irradiated skin over the period measured. (The term "maximum size of the wheal" refers to the greatest size which the wheal reached when observed over a period of 30 minutes after injection.)



GRAPH 2. RELATION BETWEEN THE SIZE OF THE HISTAMINE WHEAL AND THE TIME IN MINUTES FOLLOWING THE INJECTION OF HISTAMINE

The graph shows the difference in the rate of development of the histamine wheal on roentgen rayed skin and on non-irradiated sites. The injections were made at varying intervals from one hour to five days following the last of 3 daily roentgen ray exposures of 125 r each.

same applies to groups of readings made at two to eight days following injection. The measurements in each of these groups are averaged and are recorded under the respective columns at

the bottom of the table. The latter figures give the rate at which the average papule regressed in size when observed at daily intervals over a period of one to eight days. These results are more strikingly illustrated on graph III which is derived from the foregoing calculations. Both the table and the graph show quite definitely, that at all times during its involution the average vaccine papule in the irradiated skin is larger than its control on the non-irradiated area.

TABLE II

Differences in maximum size of histamine wheal on x-rayed and normal skin

	NUMBER OF INJECTIONS	AVERAGE READINGS	
X-ray daily 125 r × 3 (375 r):			
Histamine 0.05 cc.			
Experimental	29	15.3	
Control	29	17.8	Average experimental 15.7
Histamine 0.1 cc.			
Experimental	8	17.3	Average control 18.3
Control	8	20.1	
X-ray 125 r (single exposure), histamine 0.1 cc.:			
Experimental	20	17.0	
Control	20	18.3	
Total average readings:			
Experimental	57	16.2	
Control	57	18.3	

Vaccine papule: average size. Thirty-six injections of vaccine were made on the experimental sites and a like number of control injections on non-irradiated skin. If one notes only the greatest size which each individual papule reached when observed at daily intervals, it can be demonstrated that the vaccine papule on the roentgen rayed skin tends to be larger than on the control site. The average figures for these readings are 21.7 mm. and 18.4 mm. respectively (Table IV). However, a total of 156 readings (Table III) was made at different intervals following the injections on each of these series. The figures for the average

TABLE III

Measurements of vaccine papules

Arranged in columns of days following injection

CASE NUMBER	INTERVAL BETWEEN LAST X-RAY AND TIME OF INJECTION	CONTROL								EXPERIMENTAL							
		1	2	3	4	5	6	7	8	1	2	3	4	5	6	7	8
13	1 hour	11.0	7.0	9.5	0	0	0	0	0	11.0	8.0	7.5	0	0	0	0	0
	1 day	11.0	10.5	0	0	0	0	0	0	9.5	8.0	0	0	0	0	0	0
	2 days	10.0	0	0	0	0	0	0	0	10.5	7.0	0	5.5	0	0	0	0
	3 days	12.0	10.5	9.0	8.0	0	0	0	0	7.0	5.5	9.8	6.5	0	0	0	0
15	1 hour	11.5	—	—	—	—	—	—	—	13.0	—	—	—	—	—	—	—
16	1 hour	22.0	16.0	7.0	5.5	5.5	4.0	—	—	40.5	28.5	19.0	16.0	15.0	12.0	—	—
	1 day	26.0	19.0	17.0	6.5	9.0	—	—	—	32.0	36.0	21.5	8.5	7.0	—	—	—
	3 days	18.0	16.0	9.5	—	—	—	—	—	34.5	13.0	8.0	—	—	—	—	—
	4 days	40.5	19.0	—	—	—	—	—	—	40.5	16.0	—	—	—	—	—	—
17	1 hour	9.0	13.0	3.0	—	0	0	0	—	21.0	13.0	6.5	—	9.0	0	0	—
	1 day	15.0	7.5	—	6.0	6.0	0	—	—	15.0	21.0	—	9.5	10.0	0	—	—
	3 days	—	6.5	0	0	—	—	—	—	—	18.0	15.0	7.5	—	—	—	—
	5 days	19.0	28.5	—	—	—	—	—	—	17.0	28.5	—	—	—	—	—	—
18	1 hour	54.0	—	—	8.0	0	0	—	—	17.5	—	—	23.0	12.5	11.0	—	—
	1 day	—	—	0	10.0	0	—	—	—	—	—	11.5	11.5	0	—	—	—
	3 days	10.0	8.0	0	—	—	—	—	—	48.0	23.0	9.0	—	—	—	—	—
	4 days	45.0	8.0	—	—	—	—	—	—	51.0	8.0	—	—	—	—	—	—

19	1 hour	—	11.0	2.8	5.0	0	0	—	—	—	9.0	10.0	8.5	0	0	—	—
	1 day	10.0	2.8	6.0	0	0	—	—	—	12.0	10.5	8.5	0	0	—	—	—
	3 days	8.0	6.5	7.8	—	—	—	—	—	18.0	8.5	9.5	—	—	—	—	—
	4 days	12.0	9.0	—	—	—	—	—	—	9.0	9.5	—	—	—	—	—	—
20	3 days	15.0	13.0	7.0	—	8.0	8.0	8.0	7.0	37.5	25.5	16.0	—	10.5	22.0	19.0	10.0
	4 days	25.5	16.0	—	10.0	11.0	8.5	10.0	—	17.0	17.0	—	8.5	18.0	0	10.0	—
	5 days	9.5	—	7.5	0	0	0	—	—	25.0	—	8.5	11.0	0	0	—	—
21	1 hour	9.0	0	0	—	0	0	—	0	19.0	8.0	7.5	—	0	0	—	0
	1 day	11.5	6.0	8.5	0	0	0	0	—	9.5	9.0	8.0	0	0	0	0	—
	4 days	14.0	0	—	9.0	—	—	—	—	11.5	7.5	—	7.5	—	—	—	—
	5 days	20.0	—	9.0	—	—	—	—	—	28.0	—	7.5	—	—	—	—	—
22	1 hour	18.0	11.0	5.0	0	6.0	—	0	—	6.0	4.5	0	0	0	—	0	—
	1 day	18.0	4.0	0	3.0	—	0	—	—	31.5	12.0	6.5	0	—	0	—	—
	2 days	15.0	12.0	7.0	—	7.0	—	—	—	11.0	8.0	4.5	—	5.5	—	—	—
	4 days	14.0	—	9.0	—	—	—	—	—	17.0	—	14.0	—	—	—	—	—
23	1 hour	32.0	—	10.0	10.0	10.0	0	0	0	23.0	—	7.0	7.5	0	0	0	0
	3 days	52.0	21.0	19.0	10.0	9.5	—	—	—	31.5	25.5	7.0	8.5	7.5	—	—	1
24	1 hour	17.0	8.5	—	0	—	0	0	0	30.0	10.5	—	0	—	0	0	0
	4 days	5.5	0	0	—	—	—	—	—	6.0	7.0	0	—	—	—	—	1
Number of readings.....		33	29	26	21	21	17	11	8	33	29	26	21	21	17	11	8
Average readings.....		18.8	10.0	5.9	4.3	3.4	1.2	1.6	0.9	21.7	14.0	8.7	6.6	4.5	2.6	2.6	1.3

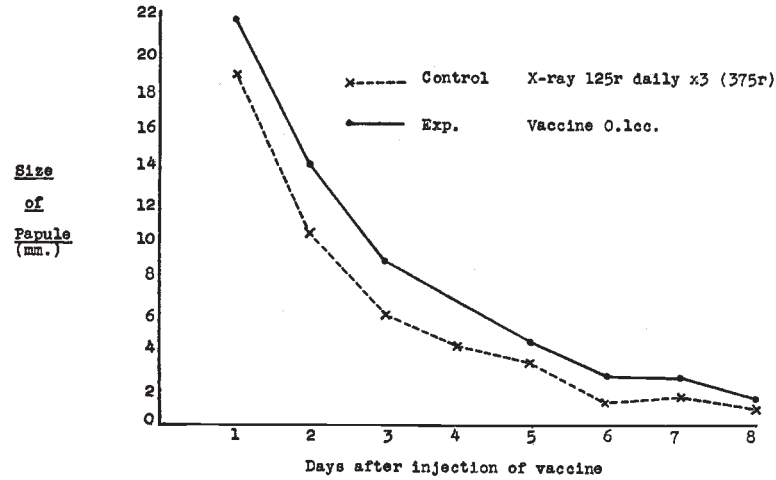
Size of papule = $\left(\frac{\text{Length} \times \text{Width}}{2}\right) \times$ Height.

0 = Zero reading. — = No reading.

Vaccine 0.1 cc. X-ray 125 r daily × 3 (375 r).

size of the experimental and control injections as based on these readings are 10.2 mm. and 8.0 mm. respectively.

Changing reactivity of the skin. In Table IV the vaccine figures are separated into groups, each group comprising papules originating from vaccine injections made at a given interval following the last roentgen ray exposure. The average figure for each group is recorded on the same table. Graph 4 is derived from these figures and depicts an interesting relationship between,



GRAPH 3. AVERAGE RATE OF REGRESSION IN THE SIZE OF THE VACCINE PAPULE AS MEASURED AT DAILY INTERVALS FOLLOWING INJECTION

Injections were made at intervals of one hour to five days following the last of three roentgen ray exposures of 125 r each. During all stages of its involution the vaccine papule is larger on the roentgen rayed skin than on the control skin. The size of the papule is calculated in millimeters from the formula:

$$\left(\frac{\text{width} \times \text{length}}{2}\right) \times \text{height}$$

on the one hand, the time of injection of the vaccine after the last roentgen ray exposure and, on the other hand, the maximum development of the vaccine papule. The graph indicates that the maximum development of the vaccine papule on roentgen rayed and non-irradiated skin may not always be the same and that the comparative difference between the two is dependent upon the interval existing between the roentgen ray exposure and the time of injection of the vaccine. In this particular

TABLE IV

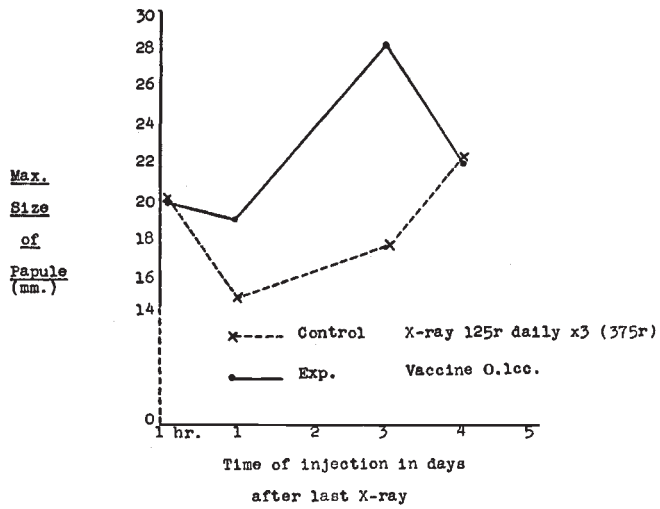
Difference in maximum size of vaccine papule on x-rayed and normal skin*

Grouped according to time of injection of vaccine after the last x-ray exposure

INTERVAL BETWEEN LAST X-RAY AND VACCINE INJECTION	CASE NUMBER	X-RAY 125 r DAILY × 3 (375 r); VACCINE 0.1 cc.			
		Maximum* size of papule			
		Experimental		Control	
		Reading	Average	Reading	Average
1 hour	13	11.0	19.7	11.0	19.9
	15	13.0		11.5	
	16	40.5		22.0	
	17	21.0		13.0	
	18	23.0		54.0	
	19	10.0		11.0	
	21	19.0		9.0	
	22	6.0		18.0	
	23	23.0		32.0	
	24	30.0		17.0	
1 day	13	9.5	18.7	11.0	14.6
	16	36.0		26.6	
	17	21.0		15.0	
	18	11.5		10.0	
	19	12.0		10.0	
	21	9.5		11.5	
	22	31.5		18.0	
2 days	13	10.5		10.0	
	22	11.0		15.0	
3 days	13	9.8	28.2	12.0	17.4
	16	34.5		18.0	
	17	18.0		6.5	
	18	48.0		10.0	
	19	18.0		8.0	
	20	37.5		15.0	
	23	31.5		52.0	
4 days	16	40.5	21.8	40.5	22.4
	18	51.0		45.0	
	19	9.5		12.0	
	20	18.0		25.5	
	21	11.5		14.0	
	22	17.0		14.0	
	24	6.0		5.5	
5 days	17	28.5	27.2	28.5	19.3
	20	25.0		9.5	
	21	28.0		20.0	
Number of readings.....		36		36	
Total average.....		21.7		18.4	

* Maximum size of papule is the greatest reading obtained on a given papule when observed over a period of 1 to 9 days.

study, at least, differences in the eventual maximal development of the vaccine papule on the irradiated and on the control skin occur only when the injections are made between the first and the third day following the last roentgen ray exposure (i.e. the fourth and the sixth day after the initial exposure). This variable result is once more in marked contrast to the differential



GRAPH 4. RELATIONSHIP BETWEEN THE MAXIMUM SIZE TO WHICH THE VACCINE PAPULE DEVELOPED AND THE TIME INTERVAL BETWEEN THE LAST OF 3 DAILY EXPOSURES OF 125 r EACH AND THE INJECTION OF VACCINE

The papule on the roentgen rayed skin reached a size greater than that on the non-irradiated skin only when injected at 1 and 3 days after the roentgen ray exposures. This, of course, indicates a variation in the reaction capacity of roentgen rayed skin (as compared to the control sites) depending on the time between the irradiation and the injection of the vaccine. ("Maximum size of papule" refers to the greatest size to which the papule developed when read over a period of 1 to 9 days.)

behavior of the histamine wheal which, under similar analysis, shows a quite constant diminution in development on the roentgen-rayed skin within the observation period of two to five days after roentgen ray exposure.

Histology. A histologic study of a vaccine papule produced on non-irradiated skin was made 48 hours after injection. This showed a rather pronounced leucocytic infiltrate, most densely

disposed about the blood vessels and glandular elements in the skin, but there was also some leucocytic infiltrate in various places tending to penetrate between the collagenous elements. While most of the cells in the infiltrate were round cells, quite a number of polymorphonuclear cells were also discovered. A slight amount of edema was present as indicated by the swelling and the separation of the collagenous fibres.

DISCUSSION

The triple response. When histamine is introduced into normal skin a triphasic phenomenon, described by Lewis (23) as the "triple response," results. The first component of this reaction is a local dilatation of the "minute vessels"[6] of the skin, resulting in a red spot at the site of the histamine injection. The second phase is a widespread dilatation of the neighboring "strong arterioles"[7] causing a bright scarlet red halo known as the flare. The third part of the triple response consists of a local increase of permeability of the walls of the "minute vessels." This results in the formation of a wheal at the site of the red spot described above. The first and third parts of the triple response are due to the direct action of histamine on the walls of the "minute vessels." The second part (i.e. the flare) results from the activation of the local axon reflex by the histamine, which in turn causes an active arteriolar dilatation. Flushing of the capillary bed supplied by these dilated arterioles then follows, and it is the distension of these minute vessels with bright arterial blood which is directly responsible for the flare.

Lewis also pointed out that any type of injury to the skin gives rise to the local formation of a histamine-like body (this hypothetical factor may be a single substance or a number of substances) which he calls "H-substance" and which results in

[6] The "minute vessels" is a term used by Lewis to indicate those small, superficial vessels of the skin which, although they include several different anatomical categories, behave in a common manner so far as the triple response is concerned. The term "minute vessels" comprises the terminal arterioles, capillaries, collecting venules, and the subpapillary venous plexuses of the skin.

[7] The "strong arterioles" is a term employed by Lewis to include the arched arterioles, the cutaneous arterial network, and the main cutaneous arteries.

reactions of the skin simulating or reproducing the triple response. Faithfulness in the reproduction of this phenomenon depends on the susceptibility of the skin to the particular type of traumatic stimulation and also to the acuteness of the injury. When an acute injury is produced, a rapid release of "H-substance" follows. This results in a high local concentration of this factor with consequent full reproduction of the triple response. In chronic injury, on the other hand, such as is induced by mild burns or freezing, or in injury with long latency such as develops after exposure of the skin to ultraviolet rays, roentgen rays, or radium, the response is quite modified because "H-substance" is slowly released and is simultaneously absorbed over a long period, so that a high concentration is never present at any one time. It is, therefore, quite obvious that in injury of the skin resulting from roentgen ray or radium exposure, the triple response is only partially developed and usually consists of redness, slight edema and only a suggestion of a flare. In fact, if this injury is sufficiently mild, clinically, at least, only slight erythema (i.e. local dilatation of the "minute vessels" of the skin) may be present.

Histamine refractory state. Lewis also has shown that if skin is injured in any way whatsoever, such as by heating, freezing, ultraviolet rays or roentgen rays, so that redness and edema result, then, when the edema subsides and only deep redness persists, its subsequent whealing reaction to histamine is either absent or greatly reduced. He showed, furthermore, that this absence of response or "refractoriness" to histamine is confined solely to the behavior of the "minute vessels" of the skin with reference to their permeability. In other words, the first two parts of the triple response are not affected, so that a histamine puncture laid down on a portion of skin prepared as described above will still produce active capillary dilatation of the "minute vessels" and an active flare; but the wheal will not appear or, at least, it will be greatly diminished in size. Lewis stated that the flare is usually of about the same extent and brightness on injured skin as when performed on normal control skin. He admits, however, that, at times, the flare is somewhat less well

developed on the injured skin. Although he does not mention specifically the development of the flare on roentgen ray or radium irradiated skin, he does state that in skin injured by freezing, the histamine flare may be greatly diminished, due, he believes, to injury to nerves of the local axon reflex.

The present histamine studies. My experiments corroborate, in general, the findings of Lewis so far as whealing reactions are concerned, and those of Zurhelle (21) with reference to whealing and also in regard to the size of the flare.

On the other hand, there is a number of respects in which my experiments amplify, more or less, the work of these investigators and in doing so shed some light perhaps on the mode of action of roentgen rays on the skin. In the first place, at no time were my roentgen ray exposures heavy enough to produce a clinically visible erythema or edema (both of which Lewis claimed were necessary for the histamine-refractory state). Moreover, my observations were made in serial fashion over a period of time following the roentgen ray exposures. In addition, most of these readings were taken before the usual clinical roentgen ray erythema appears. Furthermore, in the present studies very much larger injections of histamine were used, and in spite of the fact that the radiation doses were smaller than those of Lewis and Zurhelle, I was able to demonstrate satisfactorily a relative refractory state so far as whealing is concerned, and a definite suppression in the development of the flare in both extent and intensity.

It would appear, then, that roentgen rays absorbed by the skin result quite early in injurious changes (42) with the release of "H-substance." It seems possible that during all of the so-called clinical latent period (i.e. the time between the roentgen ray exposure and the visible erythema) the injurious changes continue presumably with an increasing rate in the release of "H-substance" until a sufficient local concentration is present to over-balance the rate of absorption and to produce sufficient capillary dilatation for the visible erythema to appear. In perhaps the initial phase after the roentgen ray exposure, the permeability of the capillaries is increased. This supposition is

supported by the interesting experiments of Mottram (41) with intravital staining, which were described above. Later (after 48 hours) the capillaries, although still dilated by the action of the "H-substance," go into a relative refractory state so far as permeability response to histamine stimulation is concerned. This, of course, is obviously relative, since if the release of "H-substance" is rapid enough and if a sufficiently high local concentration is reached, edema will eventually supervene. It is well known that if the roentgen ray dosage is high enough, edema will appear on the erythematous area. Thus Lewis found that the absolute refractory state did not occur until after the subsidence of the edema.

We have already cited reports that gross capillary dilatation has been noted by Hodes (40) and Pohle (35, 36) within several hours after roentgen ray exposures. It is obvious that changes in capillary behavior are among the earliest of roentgen ray effects and it seems quite probable that these changes may be present in a very slight degree some time before the capillary microscope can demonstrate their presence.

The experimental data here presented demonstrate that, beginning after an initial 48-hour period, the relative refractory state for histamine is maintained constantly over a period of at least four days. On the other hand, observers who have studied capillary dilatation and erythema after roentgen ray exposures are agreed that these phenomena follow a wave-like course. While our experiments were not carried out over a sufficient period of time, they appear to show that changes in permeability are not dependent on changes in dilatation of the capillaries; and that two phenomena may run a more or less independent course (see Lewis (23)).

The histamine flare. On roentgen rayed skin this is markedly reduced both in size and in intensity of erythema. Lewis accounts for the reduction of the histamine flare on injured skin by stating that the "minute vessels" in the flare area are already in a state of increased tonus due to continual flushing with blood as a result of the erythema incident to the previous injury. They, therefore, are not dilated as easily by the increased arteriolar

flow as if their tonus were not altered, with the result that the flare is somewhat reduced. Lewis admits, however, that this can account for only small reductions in the flare. It is possible that roentgen rays cause a depressant effect on the local axon reflex, since it is generally recognized that they cause analgesic effects on nerve tissue (43–47). The well known antipruritic effect of roentgen rays helps to support this argument. In this way a pronounced depression in the flare, such as we observed experimentally, might be accounted for.

The vaccine papule. In contrast to the foregoing, irradiated skin tends to react more intensely to an intracutaneous injection of stock catarrhal vaccine. Inasmuch as the histamine wheal and the vaccine papule behave in an opposite manner, one might hypothesize that different mechanisms are involved. In the case of the histamine wheal one is dealing with a mild, acute, transient injury from which the tissues make an almost complete recovery within a few hours. Here vascular permeability for fluid transudate dominates the picture. On the other hand, the injection of vaccine into the skin produces definite destructive changes in the cells of the epidermis and the upper part of the cutis resulting in a full inflammatory response in which not edema but vascular dilatation and cellular infiltrate are the prominent features. It is quite obvious, then, that even though the capillary system of the skin is in a relatively refractory state with reference to fluid permeability, this refractoriness definitely does not apply to the capacity for capillary dilatation, nor to the ability of the skin to mobilize a cellular exudate.

One can well imagine that the injury produced in the skin by roentgen ray with its accompanying protein decomposition acts as a strong chemotactic influence in stimulating the mobilization of leucocytes and wandering tissue cells. It is easy to appreciate, therefore, how, in skin already partially injured by roentgen rays, with dilated capillaries and potentially primed for cellular chemotactic mobilization, a succeeding insult (i.e. vaccine injection), which calls forth essentially a similar inflammatory response, will cause an enhanced reaction on roentgen rayed skin (summation effect).

In this connection it is interesting to note that there was at no time any clinically visible edematous component in the inflammatory vaccine papule when read after 24 hours or on succeeding days. It is of interest further to point out that most of the "late" allergic reactions such as the tuberculin, Dmelcos and the Frei tests consist not only of an infiltrated papule but there is also associated a large amount of visible edematous reaction. Undoubtedly, this accounts, in part at least, for the divergent results obtained by different investigators on the reaction of roentgen rayed skin to these substances. Zurhelle (21) found, for instance, that the Dmelcos test when read at 24 hours after injection was diminished on radium exposed skin. At this time he stated that there was much edema associated with the reaction. When the test was read again at 48 hours after injection, most of the visible edema had subsided leaving the infiltrated inflammatory papule. At this time the radium exposed skin showed a reaction of the same size as the control skin.

It appears, then, that exposure of the skin to fractional doses of roentgen rays tends to inhibit (after 48 hours) a subsequent edematous component of inflammatory reaction, while it is prone to enhance a subsequent reaction in which cellular infiltrate and vascular dilatation are the prominent features.

Roentgen rays in inflammatory states. With these facts in mind, it is interesting to speculate on the therapeutic action of roentgen rays in the treatment of inflammatory conditions of the skin. I realize, naturally, that conclusions based on the reactions of normal irradiated skin may not apply strictly to similar phenomena on skin already inflamed before irradiation. On the other hand, it seems probable that many of the differences are quantitative rather than qualitative in character. With these reservations in mind, it seemed to me that I might use the observations reported here for a theoretical analysis of roentgen ray action on inflamed conditions of the skin. Even though it is a well established fact clinically that roentgen rays produce evident benefits in inflamed states of the skin, experimental attempts to define its mode of action have thus far led to quite differing results.

It is generally agreed that roentgen radiation in the doses used in the treatment of inflammatory conditions has practically no effect on bacteria (7) or fungi (48) in vitro. It has been established also that small doses of roentgen ray have little, if any, direct action in vitro on antibodies (49) or enzymes (8). Most investigators believe that the reticulo-endothelial system may be stimulated by small doses of roentgen ray (50–53). Chrom (54), on the other hand, could not demonstrate an increased defense against bacteria after irradiation of the reticulo-endothelial system. All writers are agreed that large doses of roentgen ray depress the function of the reticulo-endothelial system.

It is possible that the direct effect of small doses of roentgen rays on granulation tissue, while generally conceded to be present, may not be great, since Pohle, Ritchie, and Wright (55), using a dosage of 1000 r in white rats, failed to show much effect on the healing of experimental wounds, especially if the irradiation was administered three days or more after the incision was made.

Mischtschenko, Fomenko, Feszenko, Lendanow, and Morgatschow (56) conclude, as result of their experimental work, that the chief effect of roentgen rays in inflammatory conditions results from the local decomposition of proteins with the release of non-specific antibodies, amino acids, and trypsin. They noted also a decomposition of leucocytes and increased phagocytosis. Desjardins (57) believes that the fundamental effect of roentgen rays in acute inflammation is due almost exclusively to rapid destruction of leucocytes in the inflammatory infiltrate with consequent release of ferments and antibodies. In chronic inflammation, he feels that the effect is not only on the leucocytes but also in a large degree on the granulation tissue. Peretz, Nevler, Mostova, and Shoshina (58) studied the effects of roentgen ray exposures on patients and on rabbits infected with staphylococci. Local roentgen ray irradiation of the infected sites failed to produce any appreciable increase in serum-antibody titre or any increase in the quantity of bacteriophage present in the pus of the irradiated lesions. When a mixture of staphylococci, serum and leucocytes was irradiated, phagocytosis was greatly increased. A similar effect was obtained following irra-

diation of staphylococcic pus. They also feel that hyperemia and increased lymph circulation are important factors in the beneficial effects of roentgen ray in inflammation.

Subsequent experiments were carried out by Nathanson (59), who used rats whose inguinal glands were infected with paratyphoid B. He was unable to demonstrate an increased bactericidal power either of the blood or the tissue after irradiation, so that he felt that roentgen rays must produce a change in tissue reaction against infection rather than a direct effect on the bacteria or on the direct bactericidal properties of the tissue or blood. On the other hand, Kissele (60) succeeded in demonstrating an increased local tissue resistance against diphtheria toxin, virulent staphylococcus, and Danysz' bacilli following fractional local irradiations in experimental animals.

Soto, Brunchwig, and Schultz (61) produced experimental infections in the skin and subcutaneous tissues of rabbits and found that while roentgen rays reduced their severity, the irradiation did not as a rule hasten the final healing. They could not demonstrate any direct effect on the leucocytic infiltrate so that they felt that the efficacy of roentgen rays in inflammation must be due to the dilatation of the capillary bed with resulting increased absorption of soluble products.

While these experimental results and conclusions at a first glance appear quite contradictory, in the light of the present experiments it seems that a common theme may exist. It also appears that the different results may be dependent upon the divergent responses of different species of experimental animals, differences in the various inflammatory agents employed, variations in the dosage, filtration, and time factors used in the roentgen ray exposures. The common denominator (metaphorically speaking) of all these observations is, in my opinion, the generally accepted fact that roentgen rays produce local injurious and destructive effects on all tissues irradiated. The amount of injury or destruction produced and therefore the type of response, depends on the dosage, filtration, intensity, and the tissue irradiated (7, 57).

For purposes of clarity it is important to define our problem by

excluding certain factors. Thus, for instance, one can state that it is pretty generally agreed that small fractional doses of roentgen ray, such as are commonly employed in the treatment of inflamed conditions of the skin and subcutaneous tissues produce a local effect only (i.e. an effect only where the roentgen ray energy has been absorbed) (56, 57, 58, 61). They do not produce a systemic response of any importance. This, of course, does not apply to higher dosages (24, 26, 62). Since in the dosages employed, roentgen rays have no direct effect on pathogenic microorganisms or on antibodies themselves, or on the direct stimulation of specific antibody formation, it is quite obvious that the benefit resulting from roentgen rays in inflammatory states must depend solely upon a nonspecific change in local tissue response.

Because it is generally conceded that the universal eventual result of roentgen ray absorption in living tissue is injury or destruction or both, it is not improbable that the change of tissue response induced by roentgen rays in inflammatory and infectious conditions results from the release of "H-substance" (Lewis) and the various products of protein decomposition. It is the latter which might account for the non-specific protein effect and the non-specific mobilization of antibodies such as was suggested by Mischtschenko and his associates (56). In other words, roentgen ray therapy is essentially circumscribed local shock therapy. But its effect is unique in that the non-specific stimulation is not a temporary transient affair, such as is the case in ordinary shock therapy, but it continues for a number of days or possibly weeks after the application of the radiant energy. Since the leucocytes in inflamed tissue are the most radiologically susceptible of all the cells present, it is not unlikely that they are the elements most rapidly destroyed (see Desjardins (57)); and these cells are very probably the most abundant source of the non-specific effect described above.

The release of "H-substance" is the complementary mechanism in this process. It is the release of the "H-substance" which is responsible for the vascular phenomenon of capillary dilatation which has been found, by direct capillary observation, to be present as early as four and six hours after a roentgen ray ex-

posure and which continues, wave-like, for a number of weeks thereafter. We have noted that Peretz and his associates (58) and Soto and his collaborators (61) attribute a major role to this vascular dilatation, in accounting for roentgen ray effects in inflammatory states. The chronic mild subclinical congestive state resulting from this capillary response may be of great importance in the carrying away of soluble noxious products from the affected area (61).

Mottram, using supravital staining, has demonstrated that increased permeability of the skin capillaries occurs at some time within the first twenty-four hour period following irradiation. Our experiments show, however, that after forty-eight hours capillary permeability for fluid transudates has fallen below normal (as indicated by the relative refractory state to histamine).

These observations are of interest because, in the first place, the initial increased permeability may well account for the flare-up or "Herxheimer-like effect"—both symptomatic and objective—that follows within a few hours after the irradiation of an inflamed site (it is to be noted that the rapid destruction of leucocytes may also be responsible for this phenomenon (57)). In the second place, the subsequent induction of the relative refractory state may play an important role in controlling the inflammatory process in the skin by limiting or inhibiting the edematous element in the diseased area.

On first thought, it would appear that the present demonstration of the increased size of the experimental vaccine papule on roentgen rayed skin, would be contradictory to all clinical evidence of roentgen ray effects on inflamed tissues. But when it is realized that the increased papule reflects an increased vascular and cellular response (as contrasted to an edematous response) of the skin, it can readily be appreciated that this type of reaction could conceivably play an important role in benefiting an inflammatory state. The experimental results here reported demonstrate that when skin is roentgen rayed a latent, if not actual, leucocytic mobilization is stimulated, enabling the skin to respond more effectively to any inflammatory insult which may be present. The latter phenomenon is probably mediated through the non-specific shock mechanism described above.

SUMMARY

It is generally agreed that roentgen rays produce destructive effects on the cellular components of the skin. Theoretically this results in the release of "H-substance" and the products of protein decomposition.

The present study of the behavior of the histamine wheal on roentgen rayed skin indicates that within forty-eight hours the permeability of the capillaries falls below normal; and this relative refractory state is maintained at a more or less constant level for a period of at least four days. From the evidence of other investigators, it may be concluded that this refractory state eventually becomes more pronounced and may even become absolute after the roentgen ray reaction has passed its peak.

The capillary dilatation which has been observed as early as four hours after a single roentgen ray exposure proceeds in a series of waves for a period of several weeks, at least.

The present study of the behavior of vaccine papules on roentgen rayed skin suggests that skin exposed to fractional doses of roentgen rays is in a state of latent, if not actual leucocytic mobilization. The chemotactic influence of the products of protein decomposition, resulting from the action of the absorbed roentgen rays on cellular protoplasm, is the mechanism which offers the most probable explanation of this effect.

It is possible that the phenomena described above are able to explain, in part, at least, the beneficial effects of roentgen rays on inflamed conditions of the skin and subcutis. A review of the literature dealing with this problem emphasizes certain facts and reveals that small doses of roentgen rays produce only a local effect on the tissue absorbing the radiation and that there is no direct effect on bacteria, antibodies, or enzymes in vitro. Most investigators agree that small doses of roentgen ray stimulate the reticuloendothelial system; but workers dealing with other phases of the inflammatory reaction are not in general agreement. These discordant results may possibly be accounted for on the basis of widely divergent conditions under which the different studies were pursued. At any rate, such factors as non-specific protein effect, non-specific mobilization of antibodies, increased blood flow, and the local destruction and mobilization

of the cellular infiltrate, were emphasized by various authors as accounting for the favorable effects of roentgen rays in inflammatory states.

It is my opinion that the changes in permeability and dilatation of the capillaries resulting from the release of "H-substance" and also the changes in the cellular infiltrative reaction of the skin due to the release of decomposed proteins with its consequent non-specific shock-protein effect are able to account for the various phenomena in the experimental investigations described above. In this way, many apparently contradictory mechanisms and results can perhaps be brought into harmony.

CONCLUSIONS[8]

(1) *The wheal,* which develops after the injection of histamine two to five days following unfiltered roentgen ray exposure (this may be a single dose or three daily doses of 125 r) tends to be *smaller on the exposed skin than on the non-irradiated site.*

(2) *The flare* which develops about the wheal when histamine is injected from one hour to five days after the last of three daily unfiltered roentgen ray exposures of 125 r *tends to be reduced in both intensity* and *size on the irradiated area as compared to the control skin.*

(3) *The papule* which develops when mixed catarrhal vaccine is injected either one or three days following the last of three daily unfiltered roentgen ray exposures of 125 r each, *tends to be larger on the roentgen rayed than on the normal skin.*

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